

USSN: 10/016,969

Amdt. Dated July 6, 2004

Reply to Office Action of March 3, 2004

REMARKS/ARGUMENTS

At the outset, Applicants wish to thank Examiner Li and Examiner Kunz for their time, patience, and assistance during a telephonic interview with the undersigned, Mi Kim, and Richard Pittner, a named inventor of the instant invention, held on June 16, 2004. Based, in part, on the discussions, Applicants submit the instant Response.

Status of the Claims

Claims 1, 8, and 33 to 54 were pending. In the instant Response, Applicants have amended claim 45. With the entry of the present amendment, claims 1, 8, 33-54 are currently pending in the application.

Support for the amendment to claim 45, wherein the method is directed to a human subject, can be found at least at page 14, lines 28-30, of the specification. Applicants submit that no new matter has been introduced by the instant amendment.

Information Disclosure Statement

Applicants thank the Examiner for considering in full and returning a signed copy of the Form 1449s filed on September 26, 2003, and January 12, 2004. The Patent Office has noted that the Applicants had cited references in a letter of September 22, 2003, and suggests that a PTO-1449 be submitted. It is Applicants' understanding that the Patent Office is referring to the Response filed Sept. 22, when it states a "letter." Applicants respectfully request correction if something other than the Response filed Sept. 22nd is meant. Applicants submit the references they wish to have considered by the Patent Office have been cited in a PTO-1449.

Issues under 35 U.S.C. §102(b)

Claims 45-47 are rejected under 35 U.S.C. 102(b) for allegedly being anticipated by Okada et al (*The Endocrine Society 75th Annual Meeting Program & Abstract*, page 180,

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Abstract 520B, 1993, herein after "Okada"). Applicants respectfully traverse this rejection to the claims as amended.

Claim 45 has been amended to be directed to a human. Claim 46 is directed to administration of peptide YY (PYY) or a PYY agonist in the amount of 0.1 ug/kg to 10 ug/kg per day. Claim 47 is directed to the PYY agonist, PYY[3-36].

Okada presented a study involving 10 week old rats given 1 nmol, 10 nmol, 20 nmol, and 40 nmol of PYY (about 4.3, 43, 86, and 172 µg, respectively) and stated that these rats did not eat as much high fat chow (58% of calories from fat) as the control rats. Assuming, as the Patent Office did, that the rats weighed 200 g, the doses taught by Okada are 21.5 µg/kg, 215 µg/kg, 430 µg/kg, and 860 µg/kg, respectively.

Claims 45-47 are not anticipated because Okada does not teach 1) the use of PYY in humans; 2) administration of PYY in the amount of 0.1 µg/kg to 10 µg/kg per day; and 3) use of PYY agonist, PYY[3-36]. Accordingly, Applicants submit that Okada does not anticipate presently pending claims 45-47. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 45-47.

Issues under 35 U.S.C. §103(a)

Claims 1, 8, 33-44, 48-50, and 52-54 are rejected under 35 U.S.C. 103(a) for allegedly being unpatentable over Malaisse-Lagae et al. (*Experientia* 33:915-917, 1977, hereinafter "Malaisse-Lagae") in view of Okada, Yoshinaga et al. (*Am. J. Physiol.* 263:G695-701, 1992, hereinafter "Yoshinaga"), and Ueno et al. (*Gastroenterology*, 117:1427-1432, 1999, hereinafter "Ueno"). Applicants respectfully traverse this rejection.

Malaisse-Lagae describes pancreatic polypeptide (PP) and its possible role in the regulation of food intake. As the Patent Office has recognized, Malaisse-Lagae fails to teach the use of PYY or PYY agonists. Okada describes reduced intake of a high fat diet by administering 1 to 40 nmol of PYY to rats. Yoshinaga describes the results of some structural studies of PYY

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on pancreatic exocrine, gastric acid, and insulin secretion. Ueno describes transgenic, overexpressing PP mice and their feeding behavior and body weight.

The Patent Office alleges that it would have been obvious for one of ordinary skill in the art at the time the invention was made to use the PYY and PYY agonist in the method of treating obesity and reducing food intake as taught by Malaisse-Lagae with a reasonable expectation of success. The Patent Office further alleges that one would have been motivated to do so because both PP and PYY decrease food intake, both belong to the pancreatic polypeptide family, and both function as an inhibitor of pancreatic exocrine.

It should be remembered that at the time the application was filed, the skilled artisan is charged with knowledge about the body of work surrounding the PP/PYY/NPY family, as well as general biological/research principles. Based on this, Applicants submit that it would not have been obvious to one of ordinary skill in the art to have substituted PYY for PP with a reasonable expectation of success.

The body of work relating to PYY and PP indicate they have very different binding profiles for receptors and biological functions. Cloning efforts have revealed a number of seven transmembrane receptors for the NPY family of peptides, all coupled through Gi, with a nomenclature of neuropeptide Y, Y1-Y6. Other binding sites have been identified by the rank order of potency of various peptides. For example, the NPY-preferring receptor has been termed Y3, but has yet to be cloned. PYY-preferring receptors have also been shown to exist (Y7). The pharmacology and distribution of these receptors has been extensively reviewed:

- Multiple receptors for the pancreatic polypeptide (PP-fold) family: physiological implications. Gehlert DR. Proc Soc Exp Biol Med. 1998 218:7-22.
- Characterization of neuropeptide Y-induced feeding in mice: do Y1-Y6 receptor subtypes mediate feeding? Iyengar S, Li DL, Simmons RM. J Pharmacol Exp Ther. 1999 289:1031-40.
- Receptors for NPY in peripheral tissues bioassays. Pheng LH, Regoli D. Life Sci. 2000 67:847-62.

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A summary, based on published data and patents available at the time of filing, of the rank order of potency of the PYY family of peptides at these receptors is given on page 10-11 (Table 1) of the application.

From the table, it can be seen that PP has a high affinity for the Y4 receptor and relatively low affinity for the other Y receptors. Conversely, PYY and NPY have low affinities for the Y4 receptor. Other than by co-localization of Y4 with another Y receptor, it would not be expected that PP would mimic the effects of PYY or NPY.

Moreover, whilst there is some overlap with other Y receptors, Y4 generally has a different pattern of distribution, implying PP's involvement in functions different from those of PYY. The Y4 receptor is highly variable across species both with regards to pharmacology and distribution, which may explain why its exact role may differ between species. In humans, Y4 mRNA is found in prostate, colon, pancreas, and small intestine as well as skeletal muscle. Lower levels of human Y4 mRNA was also found in brain by RT-PCR and Northern blot. A high level of Y4 mRNA in the rat was only found in the testis. In a more detailed study using RT-PCR, rat Y4 mRNA was found in all intestinal tissues examined with the highest levels localized to colon epithelium. Y4 mRNA has also been found in rat hypothalamus by RT-PCR and in situ hybridization. Furthermore, in situ hybridization has also detected high levels of Y4 mRNA in neurons of the rat dorsal vagal complex, area postrema, and nucleus of the solitary tract.

The highest levels of Y2 mRNA, in human post mortem brain, were found in dentate gyrus. High levels were also found throughout the cerebral cortex as well as in lateral geniculate nucleus, amygdala, substantia nigra, hypothalamus, cerebellum, and choroid plexus. Y2 is also found in the cerebral cortex, hippocampus, striatum, and amygdala. In the arcuate nucleus of the rat hypothalamus, Y2 mRNA is mainly found in NPY expressing neurons in agreement with a presynaptic function. In the rat, a similar distribution is observed with the highest levels of Y2 mRNA in hippocampal areas and in the arcuate nucleus of the hypothalamus. In the intestinal

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tract of the rat, Y1 mRNA is exclusively found in non-epithelial colon while Y2 is found in all crypt cells, villus, colon epithelium, and jejunal epithelium.

By in situ hybridization, Y5 mRNA is found in many brain regions of the rat. High levels can be found in many areas, including the paraventricular and arcuate nuclei of the hypothalamus, lateral hypothalamus, medial thalamus, suprachiasmatic nucleus, and hippocampus. A similar distribution was found in the human brain. Low levels of Y5 mRNA are present throughout the cerebral cortex of the rat. However, compared to rat and human, the overall levels of Y5 mRNA appear to be very low in mouse brain. The Y5 receptor is also found in several organs in the periphery. The highest level of Y5 expression in the periphery has been found in the testis. By RT-PCR, rat Y5 mRNA has been detected in colon crypt cells, non-epithelial colon, spleen, and pancreas.

For Y7 (GPR74), northern analysis was performed on human mRNA from heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas tissue. Expression was found in heart and brain. Lower levels of expression can also be found in lung, liver, kidney and pancreas. In situ hybridisation histochemistry reveals GPR74 mRNA expression in discrete areas of the rat brain including the amygdala (from where it was first cloned), the Purkinje and granular cell layers of the cerebellum, the piriform cortex and the hippocampus. The expression pattern is much more discrete than other known Y-receptor subtypes.

Thus, not only does PP have a vastly different binding profile than PYY, PP is expected to bind in a different tissue distribution pattern than PYY because of its preference for the Y4 receptor. The implication is that PP does not normally function and would not be expected to function like PYY. This implication is bolstered by the different biological actions of PYY and PP. For example, PYY and NPY, but not PP increase food intake after central (i.c.v.) administration.

- Peptide YY (PYY), a potent orexigenic agent. Morley JE, Levine AS, Grace M, Kneip J: Brain Res. 1985 341:200-3.

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- Characterization of neuropeptide Y-induced feeding in mice: do Y1-Y6 receptor subtypes mediate feeding? Iyengar S, Li DL, Simmons RM. J Pharmacol Exp Ther. 1999 289:1031-40.

Peripheral administration of PYY, but not PP, inhibits gastric emptying in rats (Figure 2 of the instant application) and humans. (Ueno used PP-overexpressing mice and did not exogenously administer PP).

- Lack of effect of pancreatic polypeptide in the rate of gastric emptying and gut hormone release during breakfast. Adrian TE, Greenberg GR, Fitzpatrick ML, Bloom SR. Digestion. 1981 21:214-8.
- Dose-responses for the slowing of gastric emptying in a rodent model by glucagon-like peptide (7-36) NH₂, amylin, cholecystokinin, and other possible regulators of nutrient uptake. Young AA, Gedulin BR, Rink TJ. Metabolism. 1996 45:1-3.
- Effects of peptide YY and neuropeptide Y on gastric emptying in man. Allen JM, Fitzpatrick ML, Yeats JC, Darcy K, Adrian TE, Bloom SR. Digestion. 1984 30:255-62.
- Control of gastric emptying by regulatory peptides. Ebert R. Z Gastroenterol Verh. 1988 23:165-70.
- Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the 'colonic brake' to gastric emptying. Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE. Gut. 1996 Aug;39(2):267-72.

PYY and PP have opposite effects on gastric emptying after intracisternal administration.

- Intracisternal injection of peptide YY inhibits gastric emptying in rats. Chen CH, Rogers RC, Stephens RL Jr. Regul Pept. 1996 61:95-8.
- Intracisternal injection of pancreatic polypeptide stimulates gastric emptying in rats. Okumura T, Pappas TN, Taylor IL. Neurosci Lett. 1994 178(1):167-70.

PYY, but not PP, slows intestinal transit. Studies demonstrate that PYY slows gastric emptying and intestinal transit when infused in concentrations that reproduce concentrations in blood after perfusion of the gut with fat. Release of PYY is enhanced markedly in patients with small bowel malabsorption, in whom it would serve to slow the passage of nutrients and to increase the time available for pancreatic enzymes to digest food. In addition, delayed intestinal transit would enhance nutrient absorption by increasing nutrient-mucosal contact time. Peptide YY deserves consideration as a potential mediator of the ileal brake phenomenon based on its distribution in the gut, its release by luminal fat, its enhanced release in the face of malabsorption, and its

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inhibitory effects on gastric emptying and intestinal transit.

- Effects of peptide YY (PYY) on mouth to caecum intestinal transit time and on the rate of gastric emptying in healthy volunteers. Savage AP, Adrian TE, Carolan G, Chatterjee VK, Bloom SR. Gut. 1987 28:166-70.
- Role of peptide YY in the endocrine control of digestion. Taylor IL. J Dairy Sci. 1993 76:2094-101.
- Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the 'colonic brake' to gastric emptying. Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE. Gut. 1996 Aug;39(2):267-72.
- Fat-induced ileal brake in humans: a dose-dependent phenomenon correlated to the plasma levels of peptide YY. Pironi L, Stanghellini V, Miglioli M, Corinaldesi R, De Giorgio R, Ruggeri E, Tosetti C, Poggioli G, Morselli Labate AM, Monetti N, et al. Gastroenterology. 1993 105:733-9.
- Effects of vasoactive intestinal peptide and pancreatic polypeptide on small bowel propulsion in the rat. Gustavsson S, Johansson H, Lundqvist G, Nilsson F. Scand J Gastroenterol. 1977 12:993-7.
- Effects of vasoactive intestinal peptide and pancreatic polypeptide in rabbit intestine. Camilleri M, Cooper BT, Adrian TE, Bloom SR, Chadwick VS. Gut. 1981 22:14-8.

PYY and NPY produce short-term hypertensive effects whereas PP has the opposite effect and decreases MAP.

- Peripheral modulation of duodenal and colonic motility and arterial pressure by neuropeptide Y, neuropeptide Y fragment 13-36, peptide YY, and pancreatic polypeptide in rats: cholinergic mechanisms. Wager-Page SA, Raizada E, Veale W, Davison JS. Can J Physiol Pharmacol. 1993 71:768-75.

PYY, but not PP, induces emesis in dogs.

- Identification and characterization of the emetic effects of peptide YY. Harding RK, McDonald TJ. Peptides. 1989 10:21-4.

PYY in the dorsal vagal complex, but not PP, stimulates gastric acid secretion.

- PYY-preferring receptor in the dorsal vagal complex and its involvement in PYY stimulation of gastric acid secretion in rats. Yang H, Li WP, Reeve JR Jr, Rivier J, Tache Y. Br J Pharmacol. 1998 123:1549-54.

PYY, but not PP, inhibits gastric lesions in response to ethanol.

- Intracisternal PYY inhibits gastric lesions induced by ethanol in rats: role of PYY-preferring receptors? Kawakubo K, Yang H, Tache Y. Brain Res. 2000 854(1-2):30-4.

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PYY, but not PP, inhibits field-stimulated contractions in vas deferens and epididymus and norepinephrine release in epididymus.

- Neuropeptide Y (NPY) and peptide YY (PYY) effects in the epididymis of the guinea-pig: evidence of a pre-junctional PYY-selective receptor. Haynes JM, Hill SJ, Selbie LA. Br J Pharmacol. 1997 122:1530-6.

PP is much less effective than PYY at reducing short circuit currents in rat jejunum.

- The effect of neuropeptide Y and peptide YY on electrogenic ion transport in rat intestinal epithelia. Cox HM, Cuthbert AW, Hakanson R, Wahlestedt C. J Physiol. 1988 Apr; 398:65-80.

PP is much less effective than PYY at activating rat intestinal epithelial cells.

- Peptide-YY and neuropeptide-Y inhibit vasoactive intestinal peptide-stimulated adenosine 3',5'-monophosphate production in rat small intestine: structural requirements of peptides for interacting with peptide-YY-preferring receptors. Servin AL, Rouyer-Fessard C, Balasubramaniam A, Saint Pierre S, Laburthe M. Endocrinology. 1989 Feb; 124(2):692-700.

Accordingly, while PP and PYY may share the function of inhibiting pancreatic exocrine secretion, the bulk of the literature would suggest to one of ordinary skill in the art that PP and PYY cannot be substituted for each other with a reasonable expectation of success.

The Patent Office also suggests that one of ordinary skill in the art would understand that PYY could be substituted for PP because they both belong to the same PP/PYY/NPY family. Applicants submit that it is common for family members to have very different functions. For example, amylin, calcitonin, calcitonin gene related peptide, and adrenomedullin represent a well characterized family of peptide hormones which share many common sequence elements. However their biological actions are quite diverse and not related as described below.

- The hormone calcitonin (CT) was named due to its secretion in response to induced hypercalcemia and its rapid hypocalcemic effect. It is produced in and secreted from neuroendocrine cells in the thyroid that have since been termed C cells. Calcitonin is most widely used for the treatment of Osteoporosis. (Wimalawansa SJ., Amylin,

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calcitonin gene-related peptide, calcitonin, and ADM: a peptide superfamily. Crit Rev Neurobiol. 1997;11(2-3):167-239).

- CGRP is a neuropeptide whose receptors are widely distributed in the body, including the nervous system and the cardiovascular system. This peptide seems to modulate sensory neurotransmission and is one of the most potent endogenous vasodilatory peptide discovered to date. Prolonged infusion of CGRP into patients with congestive cardiac failure has shown a sustained beneficial effect on hemodynamic functions without adverse effects suggesting a use in heart failure.
- Adrenomedullin (ADM) is almost ubiquitously expressed with many more tissues containing the peptide than not. The peptide has actions on the cardiovascular system, cellular growth, the central nervous system and the endocrine system, with a range of biological actions including vasodilation, cell growth, regulation of hormone secretion, natriuresis and antimicrobial effects. (Beltowski J, Jamroz A. ADM - what we know 10 years since its discovery? Pol J Pharmacol. 2004;56:5-27).
- Amylin is released with insulin from pancreatic β -cells in response to nutrients and other insulinogenic stimuli. Amylin's most potent actions include slowing of gastric emptying, suppression of post-prandial glucagon secretion, reduction of food intake, and inhibition of secretion of acid and digestive enzymes from the stomach and exocrine pancreas respectively. These actions point to a physiologic function of amylin to regulate the rate at which nutrients are assimilated and released into the circulation. Effects of replacement therapy in patients with absolute amylin deficiency (type 1 diabetes) or relative amylin deficiency (late type 2 diabetes). (Kruger DF, Gatcomb PM, Owen SK. Clinical implication of amylin and Amylin deficiency. Diabetes Educator 1999;25:389-398).

Accordingly, one of ordinary skill in the art, based upon studies of this family as well as others, would not believe that, just because a protein is deemed to be part of one family, it could

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be an adequate substitute for any other member of that family for any given function with a reasonable expectation of success.

Finally, the Patent Office also alleges that one of skill in the art would have been motivated to substitute PP with PYY because both PP and PYY decrease food intake. It should be noted that while Malaisse-Lagae describes PP as inhibiting food intake peripherally, PP was shown to be inactive in another study under similar conditions.

- Effects of pancreatic polypeptide, caerulein, and bombesin on satiety in obese mice. Taylor IL, Garcia R. Am J Physiol. 1985 248:G277-80.

Half of the PP-overexpressing transgenic mice died in Ueno. Moreover, no effect on body weight or adiposity was seen in Y4 receptor (PP-specific) knockout mice.

- Y4 receptor knockout rescues fertility in ob/ob mice. Sainsbury A, Schwarzer C, Couzens M, Jenkins A, Oakes SR, Ormandy CJ, Herzog H. Genes Dev. 2002 16:1077-88.

Accordingly, it was not clear from the literature that PP had an effect food intake to a degree of significance. As for PYY's ability to decrease food intake based upon Okada, Applicants remind the Patent Office that what is disclosed in Okada cannot be modified by what the Applicants teach in their application. Therefore, Okada should not be credited with teaching more than it discloses, that PYY may be a possible fat satiety factor for fat meal.

In summary, Applicants submit that one of ordinary skill in the art, considering what was known about the PP/PYY/NPY family and families of proteins in general, could not have substituted PYY for PP with a reasonable expectation of success. Moreover, there is no suggestion, in Malaisse-Lagae, Okada, Yoshinaga, Ueno, or any of the above references that PYY can be substituted for PP or the surprising discovery of PYY's potency at inhibiting food intake after peripheral administration in mice (Fig. 1 of the instant application shows the effects of PYY and PP).

On a related note, Applicants respectfully submit that reducing food intake is not necessarily linked to reduction of appetite. Food intake may be reduced for reasons unrelated to

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a reduction in appetite. For example, in gastric banding, appetite may remain unchanged while food intake is reduced. Also, a reduction in appetite may change the preference/aversion for certain foods that may or may not lead to a reduction in food intake (total caloric consumption). Accordingly, a reduction in food intake is not necessarily linked to a reduction in appetite.

Also, it was known that PYY slows intestinal transit. Delayed intestinal transit would enhance nutrient absorption by increasing nutrient-mucosal contact time and may, by this mechanism, lead to weight gain instead of weight loss. None of the references, Malaisse-Lagae, Okada, Yoshinaga, or Ueno, singly or combined, suggests that PYY could be used to reduce weight, weight gain, or increase weight loss.

Claim 51 is rejected under 35 U.S.C. 103(a) for allegedly being unpatentable over Malaisse-Lagae in view of Okada, Yoshinaga, and Ueno as applied to claims 1, 8, 33-44, 48-50, and 52-54, and further in view of Naslund et al. (*Int. J. Obes. Relat. Metab. Disord.* 23:304-311, 1999, hereinafter "Naslund"). Applicants respectfully traverse this rejection.

For the reasons stated above, claims 1, 8, 33-44, 48-50, and 52-54 are patentable over Malaisse-Lagae in view of Okada, Yoshinaga, and Ueno. Naslund does not cure the deficiencies of these references as it also does not teach, suggest or motivate one of ordinary skill in the art to substitute PYY for PP in the claimed methods with a reasonable expectation of success.

Accordingly, in light of the arguments presented above, Applicants respectfully request reconsideration and withdrawal of the rejections to claims 1, 8, 33-44, and 48-54 for allegedly being unpatentable over Malaisse-Lagae in view of Okada, Yoshinaga, Ueno, and Naslund.

CONCLUSION

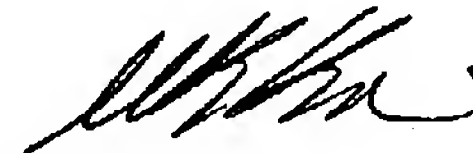
Applicants respectfully submit that the claims are now in condition for allowance and request that a timely Notice of Allowance be issued in this case. The Examiner is encouraged to

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call the undersigned attorney to discuss any issues related to the prosecution of the instant application.

Applicants believe that no additional fee is necessitated by the present paper. However, in the event any other fee is due or an amount is to be credited in connection with the instant response, Applicants authorize the Commissioner of Patents to debit or credit Deposit Account No. 010535.

Respectfully submitted,



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